A rare mutation in a patient with Noonan syndrome with multiple lentigines

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Key words: hyperpigmented skin lesions; lentigines; MAP2K1; MAPK; mitogen-activated protein kinase; Noonan syndrome; nevus; rare mutation; Ras.

INTRODUCTION

Noonan syndrome with multiple lentigines (NSML) is a rare genetic disorder that presents with multiple lentigines, intellectual disability, electrocardiographic findings, ocular hypertelorism, pulmonary stenosis, sensorineural deafness, and abnormal genitalia.[1] NSML is a spectrum of the RASopathies, which are a class of genetic syndromes caused by mutations in genes involved in the Ras/mitogen-activated protein kinase (MAPK) pathway.[2] PTPN11 is the gene most commonly associated with NSML. Other genes associated are RAF1, BRAF, and MAP2K1.[3]

Intriguingly, the hyperpigmented lesions observed in NSML can also have nevus-like features.[4] We present a 27-year-old Hispanic male who was clinically diagnosed with NSML. The patient was found to have a MAP2K1 c.305A>G (p. Glu102Gly) heterozygous pathogenic mutation; a gene commonly associated with Cardio-Facio-Cutaneous Syndrome (CFCS). To our knowledge, this is the second reported case of a patient with NSML caused by a mutation in MAP2K1, and the first reported case of a patient with NSML caused by a mutation in MAP2K1 with histologic features of junctional nevus.

Abbreviations used:

CFCS:	Cardio-Facio-Cutaneous Syndrome
ECG:	electrocardiogram
MAPK:	mitogen-activated protein kinase
NSML:	Noonan syndrome with multiple lentigines

CASE REPORT

A 27-year-old man with a past medical history remarkable for right earlobe marginal zone lymphoma, cerebral palsy, retarded growth, EKG abnormalities (incomplete right bundle branch block), dystrophic cornea, glaucoma, iritis/uveitis, retinoblastoma, and precocious puberty. The patient arrived at the clinic for evaluation and diagnosis of multiple hyperpigmented skin lesions increasing in size and number. The patient denied systemic symptoms, including: fever, chills, headache, blurry vision, oral ulcers, abdominal pain, nausea, vomiting, diarrhea, chest pain, or shortness of breath. Laboratory tests, including, complete blood count, comprehensive metabolic panel, urinalysis, thyroid function tests, vitamin D, erythrocyte sedimentation rate, c-reactive protein, antinuclear antibody, and lipid panel were within normal limits. However, an x-ray of the knees revealed diffuse osteoporosis with dysplastic changes. Chest x-ray revealed mid-thoracic dextroscoliosis. Shave biopsy of one of the hyperpigmented lesions was consistent with regular nests of melanocytes at the dermoepidermal junction (Fig 1). Salivary genetic testing was positive for MAP2K1 c.305A>G (p. Glu102Gly) heterozygous pathogenic mutation. PTPN11, BRAF, and RAF1 were negative. Physical examination was pertinent for multiple hyperpigmented lesions distributed in the face, hands, trunk, and lower extremities (Figs 2 to 4). Facial features

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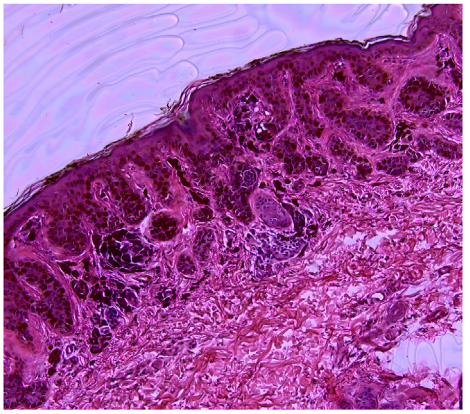

Fig 1. Hematoxylin-eosin stain. H&E: Junctional nevus (lentiginous): Dermoepidermal junction regular nest of melanocytes.

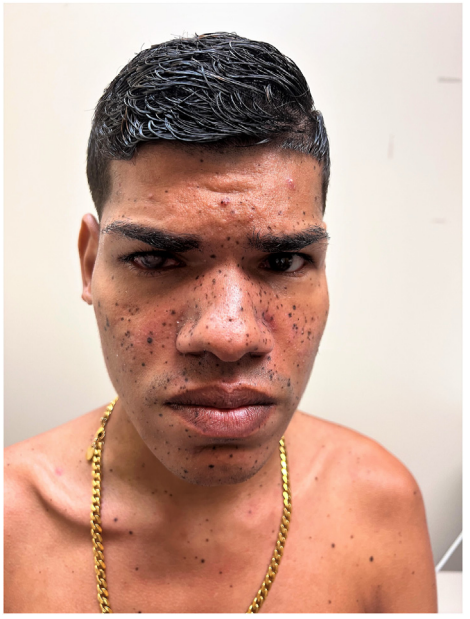

Fig 2. Noonan syndrome with multiple lentigines. Multiple hyperpigmented skin lesions scattered on the face.

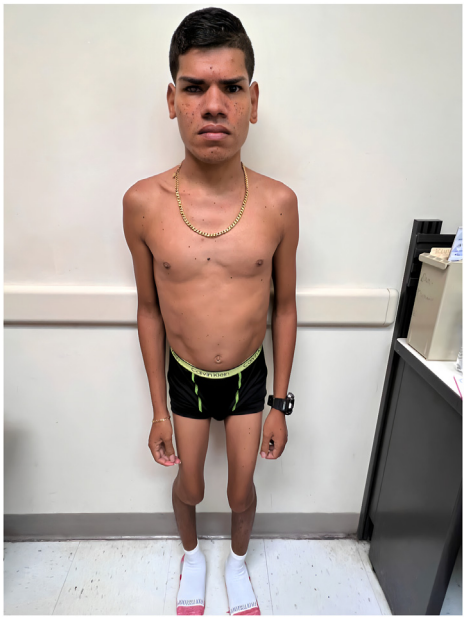

Fig 3. Noonan syndrome with multiple lentigines. Multiple hyperpigmented skin lesions scattered on the body.

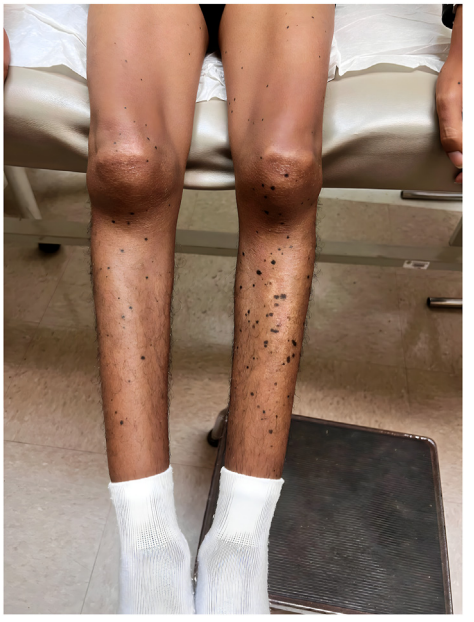

Fig 4. Noonan syndrome with multiple lentigines. Multiple hyperpigmented skin lesions scattered on the lower extremities.

included wide-set eyes. Patient also had developmental delay, broad thorax, and short stature (<10 centile); confirming the clinical diagnosis of Noonan syndrome with multiple lentigines.

DISCUSSION

The RASopathies are a category of genetic syndromes caused by mutations in genes involved in the Ras/MAPK pathway.[5] These disorders include Noonan syndrome, NSML, Carney Complex, and CFCS, among others.[5] As a consequence of the shared underlying Ras/MAPK pathway dysregulation, the RASopathies may present with a diverse range of overlapping clinical characteristics.[5] NSML diagnosis is made with clinical features only. Molecular testing is commonly done on patients with clinical features to identify the gene involved. Voron et al[6] proposed the diagnostic criteria for NSML, which includes multiple lentigines and 2 additional cardinal features. Major features include multiple

lentigines, electrocardiographic findings, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, intellectual disability, and sensorineural deafness; nevertheless, it is of paramount importance to remain aware that variable expressivity is usually observed.[6] Our patient presented with multiple lentigines, electrocardiographic findings, abnormal genitalia, skeletal abnormalities, broad thorax, and intellectual disability; he lacked ocular hypertelorism, deafness, and pulmonary stenosis.

The most common gene related to NSML is PTPN11 (> 95%). Other genes associated are RAF1 (<3%), BRAF (2 individuals), and MAP2K1 (1 individual).[3] MAP2K1 is mainly associated with CFCS.[5] Our patient neitherpresented with the characteristic structural heart defects nor characteristic facial features usually seen in CFCS patients with MAP2K1 mutations. Nishi et al[7] presented the first NSML patient with a MAP2K1 mutation. The patient was a 13-year-old Japanese boy with multiple lentigines, ocular hypertelorism, café-au-lait spots, sensorineural deafness, intellectual disability, skeletal abnormalities, and growth impairment. He lacked abnormal genitalia, electrocardiogram (ECG) findings, or pulmonary stenosis.[7]

The hallmark feature of NSML is the lentigines, which are characteristically dark in color and are small in size. In 1971, Gorlin et al[8] proposed the term "café noir spot" to describe darker and larger lentigines observed in patients with NSML; nonetheless, histological analysis was not performed. Rodriguez et al[4] described the histological features of 7 café noir spots; 3 of the lesions were melanocytic nevi, and the remaining 4 hyperpigmented lesions were lentigo simplex. The "café noir spots" seen in patients with NSML syndrome may suggest that some patients also presents with melanocytic nevi, raising the spectrum of these hyperpigmented lesions.

In conclusion, our patient could be the second individual reported to date clinically diagnosed as NSML with a MAP2K1 mutation. This case provides awareness of the genotypic spectrum of RASopathies. Although MAP2K1 mutation is a gene mostly causal for CFCS, future studies are needed to investigate further MAP2K1 mutations associated with NSML and its potential com-plications. Identifying NSML patients with this recently discovered mutation is significant as these patients have a higher risk of developing melanoma.[7] Distinctively, the histopathology of our patient with a junctional nevus, and the previous cafe noir spots suggestive of melanocytic nevi, indicate that NSML syndrome may be a condition related not solely to lentigines but also to nevi.[4,9]

Conflicts of interest

None disclosed.

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